UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,940	09/26/2006	Domenico Geraci	GRT/4161-18	1415

23117 7590 04/12/2012
NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/12/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTOMAIL@nixonvan.com
clm@nixonvan.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,940	GERACI, DOMENICO	
	Examiner	Art Unit	
	NORA ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *23,33-41,44 and 49-54* is/are pending in the application.

5a) Of the above claim(s) *33-36,40,41 and 49-54* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *23,37-39 and 44* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/20/2012 has been entered.

2. Claims 23, 33-41, 44, 49-54 are pending.

3. Claims 33-36, 40-41and 49-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/29/2009.

4. Claims 23, 37-39 and 44 are currently under examination as they read on a fusion protein characterized in that it consists essentially of allergens Parj1 and Parj2 of the Parietaria judaica species, in that each of said allergens lacks three disulphide bridges present in wild type allergens, and in that each of said allergens maintains essentially the same length as wild type allergens; wherein said fusion protein consists of the amino acid sequence of SEQ ID NO:4, pharmaceutical compositions thereof and methods of preparing a pharmaceutical composition.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 23, 37-39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Columbo et al. (IDS filed on 10/20/2010) in view of Columbo et al. (IDS filed on 08/28/2006) Bonura et al. (IDS filed on 08/28/2006) and Pauli et al. (PTO-892 mailed on 04/15/2010; Reference U).

Columbo et al. (IDS filed on 10/20/2010) teaches that Par j 1 and Par j 2 are the two major allergens in Parietaria judaica pollen which are the main cause of allergy in the Mediterranean. Parietaria pollen also contains at least 7 other minor allergens (In particular, second paragraph on page 2780). Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope (In particular, second paragraph on page 2780, first paragraph on page 2784). Colombo et al teaches Par j 1 and Par j2 allergens with substantially the same sequences as 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I). The reference also teaches loop 1 allergen mutants mutated in amino acids 1-30 of 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I) for diagnosis and therapy of pollen allergy (In particular, page 2781-2782 'Materials and Methods', sequences in Figures 2-3, whole document). Columbo et al. teaches that mutation of positions C4, C14, C29, and C30 effects structure and substitution with serine at positions 14 and 29 and deletion of position 29 leads to a decrease in IgE binding in this region (In particular, page 2782 first full paragraph, Figure 2). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (last paragraph), particularly given the importance of these allergens to allergy

in the Mediterranean and throughout the world (In particular, second paragraph on page 2780, last paragraph on page 2784). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine and 1-102 of SEQ D NO:4 (Parr j2) is the sequence for Par j 2 with C4, C29 and C30 mutated to serine.

The claimed invention differs from the prior art in the recitation of " a fusion protein characterized in that it consists essentially of allergens Parj1 and Parj2 of the Parietaria judaica species, in that each of said allergens lacks three disulphide bridges present in wild type allergens, and in that each of said allergens maintains essentially the same length as wild type allergens; wherein said fusion protein consists of the amino acid sequence of SEQ ID NO:4" of claim 23; "a pharmaceutical composition comprising the fusion protein according to claim 23 and a pharmaceutically acceptable excipient" of claim 37; "the pharmaceutical composition according to claim 37 in the form of a solution, suspension, emulsion, cream, ointment or implant" of claim 38; "and "a method for preparation of the pharmaceutical composition according to claim 37, the method comprising mixing said fusion protein in an immunologically active amount with a pharmaceutically acceptable excipient" of claim 44.

Columbo et al. (IDS filed on 08/28/2006) teaches that the Par j 1 major allergen has been shown to adopt the same structural fold with four disulfide bridges in the following order: Cys4-Cys52, Cys14-Cys29, Cys30-Cys75 and Cys50-Cys91and that the same folding has been shown for Par j 2; The immunodominant IgE epitope is located in the loop 1 region located between alpha-helixl and alpha-helix2 in the region from amino acids 1 to 30 (In particular, Table 2, page 177). The reference teaches that Cys14-Cys29, Cys30-Cys75 are the cysteine bridges that are most important for IgE binding and allergenicity (In particular, page 177, right column).

Bonura et al. teaches that Par j 1 is a major allergen in Parietaria judaica pollen and a main cause of allergy in the Mediterranean. Par j 1 allergen exhibits a high level of homology with the family of non-specific lipid transfer proteins (In particular, page 33, left column). Bonura et al teaches Par j 1 with substantially the same sequences as amino acids 105-243 of SEQ ID NO:4. The reference also teaches mutants that disrupt the cysteine bridges at C14/C29, C30/C75 and C4/C52 by mutation of those cysteine residues with serine for in vivo pharmaceutical use in a pharmaceutically acceptable excipient (In particular, page 37, right column, 'Materials and Methods', whole document). Bonura et al. teaches that mutation of positions C4, C52, C14, C29, C30 and C75 effect structure and leads to a loss of IgE binding in this region (In particular, whole document). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (In particular, discussion). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine.

Pauli et al. teaches that dimer fusion proteins of Bet v 1 in pharmaceutical compositions exhibited reduced skin reactions as determined by in vivo intradermal and skin prick testing (In particular, whole document). The reference also teaches that the dimer fusion Bet v 1 molecules had retained IgE binding capacity and fold, but microaggregation led to decreased effector cell activation (In particular, page 1081, second full paragraph). The reference suggested that pharmaceutical compositions comprising the multimers for the treatment of allergy should also contain adjuvants to prevent spreading of molecules and to decrease systemic reactions (In particular, page 1082, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of both Columbo et al. references and Pauli et al. produce a multimer fusion protein comprising Par j 1 and Par j 2 to treat allergies because Par j 1 and Par j 2 are the major allergens of Parietaria pollen. It would have been obvious to only include these two allergens since they are the two major allergens and it is desirable to produce pharmaceutical compositions which only comprise the most important allergens without the confounding effects of the seven minor allergens and other components normally present in pollen allergen extracts. By combining Par j 1 and Par j 2 into a single molecule, the molar ratio of the two allergens will be constant, thus providing a controlled dosage of both allergens to patients for optimal immunotherapy use. Because Pauli et al. teaches that dimerization of allergens does not lead to a change in the conformation of the allergen fold and Columbo et al. teaches that the 1-30 IgE epitope of Par j1 and Par j 2 is a conformational, discontinuous epitope, it would also have been obvious to perform mutational analysis at the positions taught by Columbo et al. to generate a Par j1/ Par j2 dimer protein with reduced IgE binding at that epitope. One would be motivated to do this because Columbo et al teaches that it is an important IgE epitope and because the dimer is being generated for in vivo use. It is obvious to combine two compositions which are known to have the same use. One of ordinary skill in the art at the time of invention would have been motivated to perform mutations to arrive at SEQ ID NO 4 for in vivo allergy therapy use, which may further contain an adjuvant because such a molecule would be expected to exhibit reduced IgE binding in addition to reduced effector cell activation when used in vivo to treat allergies. It would be obvious to one of ordinary skill in the art at the time the invention was made to combine the compositions of Columbo et al. and Pauli et al. because it is prima facie obvious to

combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 12/30/2011 have been fully considered, but are not found persuasive.

Applicant argues:

> "Applicants traverse because the fusion protein consisting of the amino acid sequence SEQ ID NO: 4 excludes trimeric forms such as disclosed by Pauli.
>
> If a modification proposed by the Examiner would render a prior art invention inoperable for its intended purpose, then the cited document effectively teaches away from the proposed modification and fails to establish a prima facie case of obviousness. See *In re Gordon,* 221 USPQ 1125 (Fed. Cir. 1984). Here, the modification proposed in the Office Action would change the principle of operation of Pauli. Thus, the cited combination of documents fails to establish a prima facie case of obviousness. See *In re Ratti,* 123 USPQ 349 (CCPA 1959). Therefore, Pauli cannot be relied upon to establish a case of prima facie obviousness.
>
> Finally, the Examiner is required to consider whether the improvement obtained by the present invention is more than the predictable use of prior art elements according to their established functions. See *KSR* at 1396. In Applicants' invention, the effects of the claimed heterodimer (PjEDcys) of the amino acid sequence SEQ ID NO: 4 derives from both (i) elimination of some disulphide bridges in Parj1 and Parj2 and (ii) assembly of the two modified allergens into a hybrid dimeric protein (i.e., the fusion contains two different modified allergens). The effects demonstrated in Applicants' specification would not have been predicted from the prior art. The documents cited in the Office Action (and especially not Pauli) do not make obvious Applicants' claimed heterodimer (cf. the statement on page 13 of the Office Action that

"comprising" does not exclude the use of a trimer). Here, a trimeric protein is excluded from the scope of the present claims.

The relevant inquiry for the obviousness determination is not whether *dimerization* or *trimerization* as described by Pauli could be applied to other allergens, but whether *dimerization* would be applied to Parj allergens. In other words, would it have been obvious for one of ordinary skill in the art from Pauli to consider a dimer of modified Parj allergens as a candidate for hypoallergenic immunotherapy? The conclusion would be NO! In fact, Pauli does not describe dimers and trimers as equivalent. On the contrary, the cited disclosure clearly shows that the dimer proved more allergenic in the skin pick test (see page 1082 of Pauli). Thus, a dimer is more likely to give uncontrolled allergic reactions upon injection.

For the foregoing reasons, Pauli excluded from their skin test the rBetv1 dimer and used the trimer only. Therefore, Pauli's disclosure when considered in its entirety teaches away from the claimed fusion protein, which is a heterodimer. In other words, one of ordinary skill in the art would not have found it obvious to use the claimed fusion protein over a trimeric protein with a reasonable expectation of success.

The dependent claims are also patentable over the combined disclosures do not render obvious all limitations of independent claim 23. In other words, claims 37-39 and 44 are not obvious from the cited documents because the limitations of an independent claim are incorporated in its dependent claims. M.P.E.P. § 2143.03 citing *In re Fine,* 5 USPQ2d 1596 (Fed. Cir. 1988)."

Applicant's argument that the modification proposed would render the prior art invention inoperable for its intended purpose is unpersuasive. Applicant's intended purpose of is not required. Rather, the Examiner's purpose for the resulting invention of the prior art is to be less allergenic and the combination of the references does make the resulting dimer less allergenic, contrary to Applicant's assertion. It is not necessary that the dimer be more effective than the trimer nor is it necessary to determine the most effective immunotherapy composition. Rather, the reference provides the motivation to dimerize allergens in order to decreased allergenicity for use in immunotherapy compositions.

Pauli teaches that the dimer exhibited greatly reduced basophil histamine release and did not induce wheal or flare reactions up to 1000 micrograms per ml (In particular, page 1077, left column). On page 1082, left column, the dimer was not included in the intradermal tests because it exhibited higher skin test reactivities than the trimer in the skin prick test. This teaching does

not teach away from the use of a dimer and there is no teaching in the Pauli et al. reference to suggest that the dimer is inoperable, nor that it would not be less allergenic. (In particular, see Figure 2). Whether the dimeric protein can be used more effectively is not the issue because superior effectiveness over the trimer is not required. The Pauli reference provides the motivation to make the dimeric protein.

It remains the Examiner's position that the Columbo references and the Bonura reference together provide motivation to change the conformational IgE binding epitopes of Par j 1 and Par j 2. The references highlight the important residues for structure and IgE binding and the references make it obvious to mutate and/or delete one or more of the cysteine residues involved in maintaining structure and IgE binding. One would reasonably expect that dimers of the mutated allergens would also decrease allergenicity and basophil histamine release, given the teachings of Pauli et al. Therefore, one of ordinary skill in the art would have a high expectation of success in generating the recited hypoallergenic fusion molecules.

The fact that the dimers of Pauli et al. all less allergenic though they still bind IgE and that the modifications proposed by the Columbo et al. references decrease IgE does not make the references incompatible for combination. Both references are directed to generating hypoallergic allergens. The reduction in allergenicity of the dimer is not incompatible with the reduction in allergenicity of the mutants. As such, the compositions meant for the same purpose can be combined to generate a single composition.

7. Claims 23, 37-39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (PTO-892 mailed on 04/15/2010; Reference V) in view of Colombo (IDS filed on 08/28/2006), Columbo et al. (IDS filed on 10/20/2010) and Bonura et al. (IDS filed on 08/28/2006).

Vrtala et al. teaches recombinant dimeric protein allergens of major birch pollen allergen Bet vl which exhibited profoundly reduced release of preformed (histamine)as well as de novo synthesized (leukotriene) mediators and significantly reduced IgE skin reactions (In particular, right column on page 2045 and whole document).

The claimed invention differs from the prior art in the recitation of "a fusion protein characterized in that it consists essentially of allergens Parj1 and Parj2 of the Parietaria judaica species, in that each of said allergens lacks three disulphide bridges present in wild type allergens, and in that each of said allergens maintains essentially the same length as wild type allergens; wherein said fusion protein consists of the amino acid sequence of SEQ ID NO:4" of claim 23; "a pharmaceutical composition comprising the fusion protein according to claim 23 and a pharmaceutically acceptable excipient" of claim 37; "the pharmaceutical composition according to claim 37 in the form of a solution, suspension, emulsion, cream, ointment or implant" of claim 38; "and "a method for preparation of the pharmaceutical composition according to claim 37, the method comprising mixing said fusion protein in an immunologically active amount with a pharmaceutically acceptable excipient" of claim 44.

Columbo et al. (IDS filed on 10/20/2010) teaches that Par j 1 and Par j 2 are the two major allergens in Parietaria judaica pollen which are the main cause of allergy in the

Mediterranean. Parietaria pollen also contains at least 7 other minor allergens (In particular, second paragraph on page 2780). Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope (In particular, second paragraph on page 2780, first paragraph on page 2784). Colombo et al teaches Par j 1 and Par j2 allergens with substantially the same sequences as 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I). The reference also teaches loop 1 allergen mutants mutated in amino acids 1-30 of 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I) for diagnosis and therapy of pollen allergy (In particular, page 2781-2782 'Materials and Methods', sequences in Figures 2-3, whole document). Columbo et al. teaches that mutation of positions C4, C14, C29, and C30 effects structure and substitution with serine at positions 14 and 29 and deletion of position 29 leads to a decrease in IgE binding in this region (In particular, page 2782 first full paragraph, Figure 2). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (last paragraph), particularly given the importance of these allergens to allergy in the Mediterranean and throughout the world (In particular, second paragraph on page 2780, last paragraph on page 2784). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine and 1-102 of SEQ D NO:4 (Parr j2) is the sequence for Par j 2 with C4, C29 and C30 mutated to serine.

Columbo et al. (IDS filed on 08/28/2006)teaches that the Par j 1 major allergen has been shown to adopt the same structural fold with four disulfide bridges in the following order: Cys4-Cys52, Cys14-Cys29, Cys30-Cys75 and Cys50-Cys91and that the same folding has been shown for Par j 2; The immunodominant IgE epitope is located in the loop 1 region located between

alpha-helixl and alpha-helix2 in the region from amino acids 1 to 30 (In particular, Table 2, page 177). The reference teaches that Cys14-Cys29, Cys30-Cys75 are the cysteine bridges that are most important for IgE binding and allergenicity (In particular, page 177, right column).

Bonura et al. teaches that Par j 1 is a major allergen in Parietaria judaica pollen and a main cause of allergy in the Mediterranean. Par j 1 allergen exhibits a high level of homology with the family of non-specific lipid transfer proteins (In particular, page 33, left column). Bonura et al teaches Par j 1 with substantially the same sequences as amino acids 105-243 of SEQ ID NO:4. The reference also teaches mutants that disrupt the cysteine bridges at C14/C29, C30/C75 and C4/C52 by mutation of those cysteine residues with serine for in vivo pharmaceutical use in a pharmaceutically acceptable excipient (In particular, page 37, right column, 'Materials and Methods', whole document). Bonura et al. teaches that mutation of positions C4, C52, C14, C29, C30 and C75 effect structure and leads to a loss of IgE binding in this region (In particular, whole document). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (In particular, discussion). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Par j 1 and Par j2 allergens taught by the Colombo references and Bonura et al. in the major birch pollen allergen Bet vl dimers of Vrtala et al because the dimers exhibited reduced allergenicity and can be used for diagnosis and therapy. Both Colombo et al. references teach that Par j1 and Pa j 2 can themselves be useful for diagnosis and therapy of Parietaria pollen allergy, so it would be obvious to generate dimer fusions of the allergens for

diagnosis and therapy as well. It would have been obvious to mutate both Par j 1 and Par j 2 in the same cysteine residues since Columbo et al. (IDS filed 10/20/2010) teaches that Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 12/30//2011 have been fully considered, but are not found persuasive.

Applicant argues:

> "Applicants traverse because the fusion protein consisting of the amino acid sequence SEQ ID NO: 4 excludes trimeric forms such as disclosed by Vrtala.
>
> If a modification proposed by the Examiner would render a prior art invention inoperable for its intended purpose, then the cited document effectively teaches away from the proposed modification and fails to establish a prima facie case of obviousness. See *In re Gordon,* 221 USPQ 1125 (Fed. Cir. 1984). Here, the modification proposed in the Office Action would change the principle of operation of Vrtala. Thus, the cited combination of documents fails to establish a prima facie case of obviousness. See *In re Ratti,* 123 USPQ 349 (CCPA 1959). Therefore, Vrtala cannot be relied upon to establish a case of prima facie obviousness.
>
> Finally, the Examiner is required to consider whether the improvement obtained by the present invention is more than the predictable use of prior art elements according to their established functions. See *KSR* at 1396. In Applicants' invention, the effects of the claimed heterodimer (PjEDcys) of the amino acid sequence SEQ ID NO: 4 derives from both (i) elimination of some disulphide bridges in Parj1 and Parj2 and (ii) assembly of the two modified allergens into a hybrid dimeric protein (i.e., the fusion contains two different modified allergens). The effects demonstrated in Applicants' specification would not have been predicted from the prior art. The documents cited in
> the Office Action (and especially not Vrtala) do not make obvious Applicants' claimed heterodimer (cf. the statement on page 19 of the Office Action that "comprising" does not exclude the use of a trimer). Here, a trimeric protein is excluded from the scope of the present claims.

The advantages related to preparation or formulation of the claimed fusion protein are discussed at page 5, lines 12-15, and page 7, lines 12-18 of Applicants' specification. Additional advantages are discussed below.

The relevant inquiry for the obviousness determination is not whether *dimerization* or *trimerization* as described by Vrtala **could** be applied to other allergens, but whether *dimerization* would be applied to Parj allergens. In other words, would it have been obvious for one of ordinary skill in the art from Vrtala to consider a dimer of modified Parj allergens as a candidate for hypoallergenic immunotherapy? The conclusion would be NO! In fact, Vrtala does not describe dimers and trimers as equivalent. On the contrary, the cited disclosure clearly shows that the dimer is much less effective than the trimer in skin reaction tests (see page 2045 of Vrtala).

For the foregoing reasons, Vrtala **excluded** from their skin test the rBetvl dimer and used the trimer only. Therefore, Vrtala's disclosure when considered in its entirety teaches away from the claimed fusion protein, which is a heterodimer. In other words, one of ordinary skill in the art would not have found it obvious to use the claimed fusion protein over a trimeric protein with a reasonable expectation of success.

The dependent claims are also patentable over the combined disclosures do not render obvious all limitations of independent claim 23. In other words, claims 37-39 and 44 are not obvious from the cited documents because the limitations of an independent claim are incorporated in its dependent claims. M.P.E.P. § 2143.03 citing *In re Fine, 5* USPQ2d 1596 (Fed. Cir. 1988).

It appears the Examiner contends that oligomerization of allergen would have reduced its IgE binding capacity. But this is incorrect in general. She tries to relate the hypoallergenic effects back to the decreased IgE binding of the hybrid construct, but this is contradicted by Pauli teaching at page 1081, "By contrast, the oligomeric forms of Betvl (rBetvl dimer and trimer) **retained IgE-binding capacity**" (emphasis added) and hypothesizes a different mechanism of action. Pauli also manifests surprise in finding that although the oligomers "retained the IgE binding capability, . . . unexpectedly, [they] exhibited a greatly reduced capability to induce basophil histamine release" at page 1077.

This lack of knowledge about the mechanism making an allergen construct hypoallergenic and the awareness that this effect was not mediated by a reduced IgE binding capacity, as alleged by the Examiner, is confirmed by Vrtala who affirms, "We found that E. coli expressed rBetvl monomer, dimer and trimer exhibited a comparable ability to bind IgE antibodies from allergic patients" at page 2045. As a consequence, Vrtala hypothesized possible explanations for the hypoallergenic effect (see page 2047), including "steric hindrances and unfavorable charge interactions" that are characteristics of the chemical structure of each specific allergen.

Under such circumstances, one of ordinary skill in the art would not have found it obvious to modify the disclosures of Pauli and Vrtala to chemically different allergens with a reasonable expectation of success to achieve the desired effects of Applicants' invention and its claimed fusion protein.

Applicants request withdrawal of the Section 103 rejections because the claims would not have been obvious to one of ordinary skill in the art when this invention was made with a reasonable expectation of success."

Applicant's argument that the modification proposed would render the prior art invention inoperable for its intended purpose is unpersuasive. Applicant's intended purpose of is not

required. Rather, the Examiner's purpose for the resulting invention of the prior art is to be less allergenic and the combination of the references does make the resulting dimer less allergenic, contrary to Applicant's assertion. It is not necessary that the dimer be more effective than the trimer nor is it necessary to determine the most effective immunotherapy composition. Rather, the reference provides the motivation to dimerize allergens in order to decreased allergenicity for use in immunotherapy compositions.

Vrtala et al. teaches recombinant dimeric protein allergens of major birch pollen allergen Bet vl which exhibited profoundly reduced release of preformed (histamine)as well as de novo synthesized (leukotriene) mediators and significantly reduced IgE skin reactions (In particular, right column on page 2045 and whole document). This teaching does not teach away from the use of a dimer and there is no teaching in the Vrtala et al. reference to suggest that the dimer is inoperable, nor that it would not be less allergenic. Whether the dimeric protein can be used more effectively is not the issue because superior effectiveness over the trimer is not required. The Vrtala reference provides the motivation to make the dimeric protein.

It remains the Examiner's position that the Columbo references and the Bonura reference together provide motivation to change the conformational IgE binding epitopes of Par j 1 and Par j 2. The references highlight the important residues for structure and IgE binding and the references make it obvious to mutate and/or delete one or more of the cysteine residues involved in maintaining structure and IgE binding. One would reasonably expect that dimers of the mutated allergens would also decrease allergenicity and basophil histamine release, given the teachings of Pauli et al. Therefore, one of ordinary skill in the art would have a high expectation of success in generating the recited hypoallergenic fusion molecules.

The fact that the dimers of Vrtala et al. all less allergenic though they still bind IgE and that the modifications proposed by the Columbo et al. references decrease IgE does not make the references incompatible for combination. Both references are directed to generating hypoallergic allergens. The reduction in allergenicity of the dimer is not incompatible with the reduction in allergenicity of the mutants. As such, the compositions meant for the same purpose can be combined to generate a single composition.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 25, 2012

/Nora M Rooney/

Primary Examiner, Art Unit 1644